REMARKS

Applicants note that the Examiner has withdrawn all previous rejections under 35 U.S.C. §112, 2nd paragraph, and §§102 and 103. Claims 1-53 are presently pending. Claims 30-39 have been allowed. Claims 40-48 were previously withdrawn from consideration. The sole remaining substantive rejection is this case is the Examiner's new rejection of claims 1-29 and 49-53 under 35 U.S.C. §112, 1st paragraph (written description). This new rejection was issued followed an in-person interview held with the Examiner (and Primary Examiner Bao Thuy Nguyen (Art Group 1641)) on November 3, 2005, in which the now objected to language was discussed with the Examiner and Dr. John Rush, a person of skill in the art to which the invention pertains. Applicants note the Examiner has stated these claims are free from prior arts.

Applicants have concurrently filed herewith a Notice of Appeal. No further claim amendments have been presently made. For the reasons outlined in the Remarks below, the final remaining rejection in this case is improper and unsustainable, and should therefore be withdrawn.

DOUBLE-PATENTING (STATUTORY) REJECTION

The Examiner has maintained the provisional rejection of claims 1-29 under 35 U.S.C. §101 for "statutory" double patenting, as allegedly claiming the same invention as that of claims 1-29 of co-pending application USSN 10/175,486 (Rush *et al.* -- also owned BY CELL SIGNALING TECHNOLOGY, INC., the assignee of the present application).

Since the rejection is provisional, Applicants respectfully request that this rejection be held in abeyance until such time as the present application or cited co-pending application issues as a patent, at which time Applicants will cancel or amend any identical claims in the remaining application.

§112, 1ST PARAGRAPH, WRITTEN DESCRIPTION REJECTIONS

The Examiner has newly rejected claims 1-29 and 49-53 under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description. The Examiner asserts that one of skill in the art to which the invention pertains would not recognize that Applicants had possession of the claimed subject matter because the term "naturally-occurring" (with respect to post-translationally modified peptides) does not appear explicitly anywhere in the specification. Applicants submit the rejection is improper and not supported by any evidence, and should be withdrawn.

a. The Examiner has Failed to Establish the Required Prima Facie Showing of Insufficient Written Description.

There is *a strong presumption* that an adequate written description of the claimed invention is present when the application is filed. *See* MPEP §2163(A), *citing In re Wertheim* (CCPA 1976); *see also* U.S.P.T.O. Revised Interim Written Description Guidelines Training Materials (April 2000), at page 4. *The initial burden is on the Examiner* to present *evidence or reasons* why a person skilled in the art would not recognize that an applicant is in possession of the claimed invention. *See* MPEP §2163(II)[A]; MPEP §2163.04; *see also* Written Description Guidelines, *supra.*

An Examiner must carry this burden by a preponderance of the evidence, and must set forth express findings of fact to support an allegation of inadequate written description. *See* MPEP §2163.04. Again, the MPEP stipulates that a general allegation of lack of written description is *not* a sufficient reason to make or support a written description rejection. *See* MPEP §2163(III)(A). Similarly, the lack of an express definition or term in the specification is not an acceptable basis on which to make a written description rejection. *See* MPEP §2163.02; *see also* Written Description Guidelines, *supra.* ("The absence of definitions or details for well-established terms or procedures should *not* be the basis of a rejection under 35 U.S.C. §112, para. 1, or lack of adequate written description.")

In the present case, the Examiner has failed to provide *any* evidence or facts (much less a preponderance) supporting why one of ordinary skill in the mature and developed art of post-translational protein/peptide modification and signal transduction would fail to recognize possession of the claimed method as of the filing date of the application. No express findings of *fact* have been presented. No *evidence or supportable reasoning* has been adduced to support the cursory allegation that possession is not established. Indeed, the required initial showing is not possible based on the mature state of this art and the evidence of record in this case (including review articles of post-translational proteomic methods).

Accordingly, the Examiner has erred by failing to establish the required *prima facie* showing of inadequate written description. The new rejection of claims 1-29 and 49-53 is therefore improper, and should be withdrawn.

b. The Examiner has Misapplied an Explicit Term Support Requirement that Does *not* Exist under U.S. Patent Law or Rules.

It is firmly and clearly established under U.S. patent law that literal or "*in haec verba*" claim term support is not required to establish possession of a claimed invention, nor is presence or absence of such literal support the appropriate test for adequacy of written description. *See* MPEP §2163.02. The Federal Circuit has repeatedly made this point crystal clear, for example see:

In re Kaslow, 217 U.S.P.Q. 2nd 1089 (Fed. Cir. 1983) ("The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession . . . rather than the presence or absence of literal support in the specification for the claim language.")

Fujikawa v. Wattansin, 39 U.S.P.Q. 2nd 1895 (Fed. Cir. 1996) ("*Ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question.")

Perdue Pharma L.P. v. Faulding Inc., 56 U.S.P.Q.2nd 1481 (Fed. Cir. 2000), and *Crown Operations Int'l., Ltd. v. Solutia, Inc.*, 62 U.S.P.Q.2nd 1917 (Fed. Cir. 2002) ("In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue.")

All Dental Prodx, LLC v. Advantage Dental Products, Inc., 64 U.S.P.Q.2d 1945 (Fed. Cir. 2002) ("In order to comply with the written description requirement, the specification need not describe the claimed subject matter in exactly the same terms as used in the claims; it must simply indicate to persons skilled in the art that . . . the applicant had invented what is now claimed.")

The MPEP also makes this crystal clear, stating "The subject matter of the claim need not be described literally (*i.e.* using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." See §2163.02

In the present case, the Examiner has nonetheless misapplied an explicit *ibsis verbis* test to Applicants' specification and claimed invention, and has improperly based the new written description rejection on nothing more than the absence of *literal* support in the specification for the precise phrase "naturally-occurring." The Examiner has provided *absolutely no other basis* for why the 119-page specification, as filed, would not convey to the skilled artisan that Applicants possessed

the claimed subject matter. This error is all the more striking considering that the entire specification, from the first paragraph in the Background of the Invention through the Examples, makes it exceedingly clear to the skilled artisan that the claimed invention pertains to isolating and characterizing naturally-occurring, biologically-relevant, post-translational protein/peptide modifications that occur in signaling pathways, rather than artificial and non-biologically relevant protein alterations and tags made by man to assist in purifying proteins.

Accordingly, the Examiner has erred by failing to apply the proper written description analysis and misapplying an improper *ipsis verbis* test to support an assertion of inadequate written description. The new rejection of claims 1-29 and 49-53 is therefore improper, and should be withdrawn.

c. The Examiner has Failed to Construe the Specification and Claims from the Eyes of the Skilled Artisan and Has Disregarded Evidence of High Skill in this Mature Art.

To satisfy the written description requirement, a specification must convey to one of skill in the art to which the invention pertains that the inventors were in possession of the claimed invention at the time of filing. *See* MPEP §2163(3)[a], *citing Purdue Pharma L.P. v. Faulding* (Fed. Cir. 2000); *see also* MPEP §2163.02. Stated a different way, the test is whether one of skill in the art (*not* an examiner) would recognize, based on the disclosure, that the inventors invented and possessed the subject matter now claimed. *See, e.g. Gentry Galley v. Berkline Corp.*, 134 F.3d 1473 (Fed. Cir. 1998), *citing In re Gostelli* (Fed Cir. 1989)).

In assessing whether adequate written description is provided in the specification, an examiner must view the disclosure from the standpoint of one skilled in the relevant art, giving due weight to the level of skill and knowledge in that art, and the level of advancement of the art. Indeed, the MPEP states "Such a review is conducted from the standpoint of one of skill in the art . . . and should include a determination of the field of the invention and the level of skill and knowledge in the art." §2163(II)(A)(2), *citing Wang Labs v. Toshiba Corp.*, 993 F.2d 858 (Fed. Cir. 1993) (emphasis added). The level of knowledge in, and state of, the relevant art is so important to the assessment of possession that the MPEP instructs:

> "Patents and printed publications in the art should be relied upon to determine whether an art is mature and what the level of knowledge and skill is in the art. In most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification disclosed only a method of making the invention and the function of the invention." §2163(II)(A)(3)(a)(i), *citing in re Hayes Microcomputer Products, Inc. Patent Litigation, 982*

F.2d at 1527 (Fed. Cir. 1992).

In the present case, printed publications together with the evidence of record indicate that the art to which the invention relates – the study of post-translational modification of proteins/peptides in biological cells and methods for isolating the same – is a mature art, where the level of skill and knowledge is very high. The advanced knowledge in this art strongly supports the sufficiency of the written description provided by the inventors in the detailed 140-page specification as filed.

I. The Level of Skill and Knowledge in the Art.

First off, consideration of publications and printed matter to assess the state of the art, as required, readily indicates that the art to which the invention pertains is well established. The study of post-translational modification of proteins in cells after they are expressed, as a field, has been around for many decades. These critical and well known biological processes are described in even *basic* texts (well below the level of the skilled artisan) in the area of biochemistry and molecular biology. For example:

In BIOCHEMISTRY, Zubay (1983), Addision-Wesley Publishing Co. Inc., a section entitled "Final Adjustments: Posttranslational Modifications" (Chapter I, page 29) teaches:

> "Posttranslational modification of proteins has become an area of intense study in recent years, and it would appear that few proteins are in a finished state as they roll off the ribosomal 'assembly line.' The newly synthesized protein may undergo a variety of changes in its life as an active biological entity. [] The more that is learned about the details of protein structure, the more extensive becomes the catalogue of posttranslational modifications. These modifications include the covalent attachment of carbohydrate, lipid, nucleic acid, phosphate, sulfate, carboxyl, methyl, acetyl, and hydroxyl functions. Proteins so modified are endowed with new functional capabilities in terms of binding and catalysis, regulation, physical properties, and so on."

Similarly, in BIOCHEMISTRY, 3rd Ed., Stryer (1988), Freeman & Co., it is taught (Chapter 33, page 824) in a section on DNA interaction with histones, that:

> "Each type of histone can exist in a variety of forms because of post-translational modifications of certain side chains. [] Histones can be methylated, ADP-ribosylated, and phosphorylated. The modulation of the charge, hydrogen-binding capabilities, and shape of histones by these reversible covalent modifications may be important in packaging DNA and in regulating its availability for replication and transcription."

Another illuminating example is MOLECULAR BIOLOGY OF THE CELL, 4th Ed., Alberts *et al.* (2002), Garland Science, Inc., which goes so far as to specifically define (see Glossary G:28) a "posttranslational modification" as:

> "The enzyme-catalyzed change to a protein made after it is synthesized. Examples are acetylation, cleavage, glycosylation, methylation, phosphorylation, and prenylation."

Yet another illuminating example is STRUCTURE IN PROTEIN CHEMISTRY, Kyte (1995), Garland Publishing, Inc., a text that contains a detailed section on "Posttranslational Modification" of proteins (see pages 93-103) and teaches:

> "The covalent structures of many proteins, however, do not remain in this untouched state but are biologically modified. A posttranslational modification is any change in the covalent structure of a polypeptide that occurs after its emergence from the ribosome. Some of these modifications of the original covalent structure are performed by proteolytic enzymes. *These normal modifications must be distinguished from artifactual modifications that occur, for example, during the purification of a protein.* [] There are many posttranslational modifications that have been isolated from *naturally-occurring* polypetides." (emphasis added)

This section goes on to discuss the many types of naturally-occurring posttranslational modifications of proteins in cells, which are summarized in a table and include phosphorylation, sulfation, carboxylation, aromatic substitution, methylation, acylation, monooxygenation, ADP-ribosylation, nucleotidylation, and glycosylation.

Clearly, even these basic biological textbooks establish that not only skilled artisans in the field to which the invention pertains, but any student of basic biological science, appreciate what a post-translational modification to a protein or peptide is and that such modifications are naturally-occurring (or *in vivo*) as part of normal biological/cellular processes (as opposed to artifactual or made-man modifications).

Next, going beyond the basic understanding evidenced by these textbooks to consider publications that establish the state of the art for skilled artisans, it is even more clear that the level of knowledge and skill in this mature art is very high. For example, an entire 30+ page chapter on "In Vivo Chemical Modification of Proteins (Post-Translational Modification)" in *Ann. Rev. Biochem 50:* 783-814 (1981) is dedicated solely to this topic. This detailed publication begins, in its Introduction, by stating that "Numerous reviews of individual *in vivo* modification reactions (phosphorylation, glycosylation, methylation, etc.) have been written during the last several years . . ." Thus, this article builds on *many years of knowledge* of posttranslational protein modification that

accrued prior to 1981. It also states, in its introductory paragraphs, that "an attempt has been made [in the paper] to develop some broad classes of biological functions served uniquely by *in vivo* protein modifications." The paper then goes on to review in detail all then-known *in vivo* posttranslational modifications of amino acids, including methylation, phosphorylation, and many other types of naturally-occurring biological modifications.

There is further an *entire 365-page textbook* entitled SIGNAL TRANSDUCTION, Heldin & Purton Eds. (1996), Chapman & Hall press, that is specifically dedicated to the role naturally-occurring post-translational modifications to proteins plays in signal transduction mechanisms within cells. In 23 distinct chapters, this textbook details the different classes of *in vivo* cellular signal transduction proteins and the post-translational modifications that regulate their activity and function. Clearly, these publications (and others like them), establish that the meaning and scope of "post-translational modification" are crystal clear to those of skill in this art, and that such artisans know these modifications are "naturally-occurring" (or *in vivo*) and relevant to biological signal transduction processes (as opposed to artifactual or artificial/man-made modifications which are not relevant to natural biological processes). Indeed, "post-translational modification" is a term of art that is understood to mean those that are naturally-occurring.

In fact, prior to the filing of the present application, many companies began commercially focusing on providing research reagents to study how post-translational modifications affect cellular signaling pathways and disease, and providing these reagents to skilled artisans in this field. Examples are Upstate Biotechnology, Inc., Santa Cruz Biotechnology, Inc., and Cell Signaling Technology, Inc. (the assignee of the present application). By way of example, in the 2000-2001 Cell Signaling Technology, Inc. Catalogue & Technical Reference, a resource well known to those of skill in this art, the following introductory summary about post-translational modification and biological signaling is provided (at page 10):

> "Underlying essentially all human disease are defects in cellular communication and control. These processes are mediated in large part by post-translational modification, enabling rapid changes in cellular physiology in response to environmental and cellular cues. Protein modifications including phosphorylation and acetylation can serve as molecular "switches" that dynamically regulate enzymatic activity and protein-protein interactions. The intracellular signals that propagate these modifications are frequently amplified and expanded through cascades of sequential phosphorylation events. These 'signal transduction pathways' determine how a cell will respond to a given stimulus, and correspondingly aberrations in the function of signaling kinases and other related molecules have been implicated in an extensive array of diseases."

Clearly then, those of skill in the art to which the present invention pertains appreciate what post-translational modifications are, that they are naturally-occurring in biological cells, that such modifications are a major mechanism by which cells control their processes, and that aberrations in such post-translational modification mechanisms lead to disease.

The mature state of this art and the high level of knowledge of the skilled artisan is further underscored and evidenced by publications in the field that review the state-of-the-art in post-translationally modified protein/peptide isolation methods prior to the filing of the instant application. Two such references, Quadroni *et al.*, "Phosphopeptide Analysis", *Proteomics in Functional Genomics 88:* 199-213 (2000) (cited as Ref. DA)), and Mann *et al.*, *Trends in Biotech. 20:* 261-268 (2002) (cited and discussed in the Background (Ref. CG)) (hereinafter "Mann"), have previously been specifically cited and discussed by Applicants during prosecution of the present case, and were discussed with the Examiner in-person during the interview held on November 3, 2005. In particular, Quadroni (Ref. CG) illuminates the mature nature of the art and high level of skill possessed by the artisan familiar with post-translational modifications in biological systems.

Quadroni (Ref. DA) is a review article of phosphopeptide analysis techniques discussing and representing the state of the art around the time of the present invention. This review paper starts off by stating, in its Introduction:

> "Protein phosphorylation has emerged, since its discovery over 4 decades ago, as the main mechanism by which cells modulate enzyme activity and protein-protein interactions. It is estimated that as much as one-third of the protein expressed in a typical mammalian cell may be phosphorylated at some stage during the life of the cell. Virtually all aspects of a cell's activities appear to be regulated by phosphorylation: (i) cell proliferation and differentiation, (ii) cell survival/programmed cell death, (iii) cell cycle progression, (iv) cell shape and adhesion, (v) protein secretion, (vi) endocytosis and phagocytosis, and (vii) chemotactic and sensory events."

From this review publication, and the other publications and texts discussed above, it is clear that (i) the study of post-translational modifications to proteins/peptides is a mature field with a high level of skill in the art, and (ii) that those of skill in this art readily appreciate that *in vivo* (or naturally-occurring) post-translational modifications, such as phosphorylation and acetylation, are important because they are critical to regulatory events in biological cells that lead to disease when disrupted.

Indeed, it is the development of a novel and powerful method to approach this study (on a cell-wide or proteome-wide basis) that is the problem solved by the invention. For example, Mann

(Ref CG), a review of peptide isolation and phosphoproteomic mass spectrometry approaches authored by one of the recognized leaders in the field, summarized the need in the art for better methods to study cell-wide or global post-translational modifications to proteins/peptides by stating, it its summary abstract:

> "In signal transduction in eukaryotes, protein phosphorylation is a key event. To understand signaling processes, we must first acquire an inventory of phosphopeptides and their phosphorylation sites under different conditions. Because phosphorylation is a dynamic process, elucidation of signaling networks also requires quantitation of these phosphorylation events."

This need in the art for better methods of studying diverse populations of naturally-occurring (or *in vivo*) post-translationally modified peptides/proteins on a cell-wide basis – in order to get a "snapshot" of signaling pathways in a given cell at a given time – is the very need filled by the present invention.

II. The Description Provided in the Specification.

Against this backdrop of extensive knowledge and skill in this mature art, the Applicants filed a 140-page, very detailed specification describing their invention (as presently claimed) – a new and powerful method for quickly isolating, and optionally characterizing, a target population of naturally-occurring post-translationally modified peptides from a complex mixture of peptides (the complex mixture, for example, potentially also containing many other types of modified peptides and unmodified peptides that are not desired to be isolated). The invention solved the need in the art for a new method suitable for studying *in vivo* post-translationally modified peptides/proteins in a given cell or tissue, at a given time, on a proteome- or cell-wide basis.

Right from the first pages of the specification, it is clear that Applicants' invention relates to naturally-occurring post-translationally modified peptides, and not artificial or man-made ones (such as employed in techniques for tagging and purifying a given protein). For example, the first paragraph of the Background (page 1, lines 14-24) starts out by stating:

> "The activation of proteins by modification represents an important cellular mechanism for regulating most aspects of biological organization and control, including growth, development, homeostasis, and cellular communication. [] In spite of the importance of protein modification, it is not yet well understood at the molecular level. The reasons for this lack of understanding are, first, that the cellular modification system is extraordinarily complex, and second, that the technology necessary to unravel its complexity has not yet been fully developed."

After discussing the limitations of prior art techniques, the Background of the specification concludes by stating (at page 6, lines 21-28):

> "Accordingly, there remains a need in the art for the development of simple peptide isolation/purification methods that are suitable for the isolation of modified peptides from complex mixtures of peptides, e.g. digested cell extracts, which contain a wide variety of different, modified proteins [] The development of suitable peptide isolation methods that are simple and can be readily automated would, for example, enable the rapid profiling of activation states on a genome-wide basis and the identification of new diagnostic or therapeutic targets within cell signaling pathways that are at the forefront of the proteomics era currently underway."

Right from the beginning of the specification, then, it is clear to the skilled artisan knowledgeable in this field that the invention relates to methods for isolating post-translationally modified peptides *that are relevant to cellular processes and thus are naturally-occurring in biological systems* (*i.e.* the modifications are those that occur *in vivo*).

This focus on the invention is described in extensive detail throughout the rest of the specification. The Detailed Description begins by stating (on page 19, lines 10-14) that "In accordance with the present invention, there is provided a general method for isolating a modified peptide (derived from a post-translationally modified protein) from a complex mixture of peptides, such as a digested cell lysate." The first step of the method is described as "(a) obtaining a proteinaceous preparation from *an organism* . . ." (emphasis added). The skilled artisan in the field clearly understands from this description that the invention is directed to isolating naturally-occurring (not artificial) post-translationally modified peptides.

The specification goes on to describe (at page 19, lines 9-18) that:

> "The method of the invention enables the single-step isolation (and subsequent characterization) of multiple different modified peptides, corresponding to a multitude of different modified proteins and signaling pathways, with a single antibody. The method is, therefore, suitable for genome-wide (*e.g.* cell-wide or organism-wide) profiling of activation states, and is readily automatable. The method allows, for example, the rapid, cell-wide profiling of modification states, such as phosphorylation, of many different proteins in a test cell or fluid (*e.g.* a diseased cell) as compared to a reference cell or fluid (*e.g.* a normal fluid from a healthy organism)."

Clearly then, the skilled artisan appreciates from reading the specification that the claimed invention is directed to isolating, from a complex mixture taken *from a biological system*, naturally-occurring post-translationally modified peptides that provide a "snapshot" of modification states in that system. The same artisan appreciates that the invention is not directed to non-naturally-occurring modifications to proteins, such as the type introduced by man to tag and purify proteins, which

artificial modifications are *not relevant* to normal cellular signaling processes. Again, *see* STRUCTURE IN PROTEIN CHEMISTRY, Kyte (1995), *supra.* "These normal modifications must be distinguished from *artifactual modifications* that occur, for example, during the purification of a protein. [] There are many posttranslational modifications that have been isolated from *naturally-occurring* polypeptides." (emphasis added)).

Nonetheless, the specification continues to describe and show possession of the invention in further detail. An express definition is provided (at page 22, lines 17-24) of what a "modified peptide" means:

> " 'modified peptide' means a peptide having an amino acid sequence comprising at least one, but alternatively more than one, post-translationally-modified amino acid, for example (but not limited to), a phosphorylated amino acid such as phosphotyrosine, phosphoserine, or phosphothreonine, or an acetylated amino acid, such as acetyl-lysine; modified peptides may contain multiple modified residues of the same type (*e.g.* two or more phosphorylated residues) or may contain multiple modified residues of differing type (*e.g.* a phosphorylated residue and a glycosylated residue)."

Still further, an express definition of what the "proteinaceous preparation" from which the post-translationally modified peptides are isolated is also provided (at page 23, lines 3-6):

> " 'proteinaceous preparation' means a preparation of proteins and/or peptides from one or *more cells, tissues, or biological fluids of an organism*, whether unpurified or purified (e.g. IMAC pre-purified), for example a crude cell extract, a proteolytic digest, serum, and the like" (emphasis added).

From these two definitions, together with the rest of the specification, it is crystal clear to the skilled artisan that the inventive method described, claimed, and possessed by Applicants is directed to isolation of naturally-occurring (*in vivo*) post-translationally modified peptides taken from biological systems, because those are the type of peptides relevant to obtaining a "snapshot" of global protein modification in a cell or tissue.

The specification goes further, however, to describe in great detail over five-and-a-half pages (see pages 24-30) how proteinaceous preparations containing post-translationally modified peptides are obtained from biological organisms and tissues. The importance of doing so in order to isolate naturally-occurring modified peptides relevant to signaling in those biological samples is highlighted (at page 25, lines 8-10), "The use of such living tissue allows direct analysis of the biological state of the tissue without introducing artifacts that may arise as a consequence of growth in culture." The specification also describes (at page 25, lines 4-6) that, "Preferably, proteinaceous preparations are

obtained so as to reflect the baseline, *in vivo*, activation state, e.g. phosphorylation state, of proteins in a given cell . . ." And still further, the specification (at page 28, lines 21-27) states:

> "Accordingly, these complex mixtures of modified peptides reflect the activation state, *e.g.* phosphorylation state, of signaling pathways in a given organism or cell type on a genome-wide or cell-wide basis, *thus providing a snap-shot of activation states in that organism.* The complex mixture of modified peptides in the proteinaceous preparation reflects the baseline, *in vivo* activation status in the given organism or cell line, but may, as discussed above, reflect activation status in a treated cell, so as to reflect the effect of treatment upon activation status." (emphasis added)

These sections, as well as the rest of the specification generally, hammer home that the method disclosed, described, and possessed by Applicants is directed to isolating naturally-occurring post-translationally modified peptides from biological systems in order to get a view of the global *in vivo* modification states of a desired population of proteins/peptides. In fact, the specification further describes in vivid detail, over 5 pages (pages 60-64), how the method invented and possessed by Applicants may be applied, *inter alia*, to study "modifications in a given organism" and "to determine how global protein modifications changes within a given cell or tissue in response to environmental changes, such as stress, inflammation, disease, drug treatment, etc."

In addition to this, the specification describes in detail the types of naturally-occurring post-translational modifications to which the invention relates, which are already well known to those of skill in the art. *See*, for example, pages 22, lines 17-24; page 28, lines 15-19; and p. 38, lines 12-15. These post-translational modifications, which include phosphorylation, acetylation, glycosylation, and methylation are all naturally-occurring (*in vivo*) post-translational modifications, are well known to those of ordinary skill in the art, as evidenced by the publications discussed above. Indeed, all of the 12 Examples provided by Applicants (described in detail on pages 66-130 of the specification) describe the isolation of naturally-occurring post-translational modifications that occur *in vivo* in biological systems.

In summary, conducting the required assessment (by consulting publications in the field) of the level of skill and knowledge in the field to which the invention relates, and then reading the detailed 140-page specification through the eyes of such skilled artisan inevitably leads to the following conclusion: One of ordinary skill in the art would recognize that the Applicants possessed, at the time the instant application was filed, the described and presently-claimed method for isolating a population of naturally-occurring post-translationally modified peptides from a complex mixture of

peptides (which mixture is obtained from a proteinaceous preparation obtained from an organism). The specification therefore satisfies the written description requirement. Accordingly, the Examiner's unsupported assertion to the contrary and the outstanding written description rejection are improper and unfounded, and the new rejection of claims 1-29 and 49-53 should be withdrawn.

In fact, the Examiner's unsupported assertion is also directly contradicted by another piece of evidence in the record. On November 3, 2005, Applicants attorneys conducted an in-person interview with the Examiner, which interview was also attended by Primary Examiner Bao Thuy Nguyen (Art Group 1641) and Dr. John Rush, Ph.D. (the first named inventor on the present application), who is a person of skill in the art to which the invention pertains. During the interview, Dr. Rush discussed the state and shortcomings of the art existing at the time the present application was filed, and how these shortcomings were solved by the method of the invention. Several prominent review articles (including the Mann and Quadroni references discussed above) establishing the state of the art were discussed. Certain claim amendments, including the introduction of the phrase "naturally-occurring" before "post-translationally modified peptides" were also discussed, which amendments were made to more distinctly point out the characteristics and features of the claimed subject matter.

Specifically, Dr. Rush, the skilled artisan, discussed that the types of post-translationally modified peptides described in the specification and well known in this art are "naturally-occurring" (or *in vivo*), as opposed to being man-made or artificial and thus not relevant to signal transduction in biological systems (this position is supported by standard publications in the field as discussed above; again, *see* STRUCTURE IN PROTEIN CHEMISTRY, Kyte (1995), *supra*. "These normal modifications must be distinguished from *artifactual modifications* that occur, for example, during the purification of a protein. [] There are many posttranslational modifications that have been isolated from *naturally-occurring* polypeptides." (emphasis added)). Hence, Applicants agreed during the interview to make that amendment in order to make explicit the characteristics and features of the claimed invention that would already have been understood by the skilled artisan. Dr. Rush discussed that, in contrast to the method of the invention, certain prior art techniques previously cited by the Examiner related to isolating *man-made* (or artificial) modifications introduced into proteins to tag them for purifications. The Examiner's Interview Summary Record acknowledges this point. Nonetheless, the Examiner subsequently disregarded the testimony given by Dr. Rush, a skilled artisan in the field, and made the new and unsupported assertion that a skilled artisan would

somehow not recognize Applicants possessed the claimed method for isolating naturally-occurring post-translationally modified peptides from a complex mixture.

Conclusion

For the reasons set forth above, the sole outstanding written description rejection of claims 1-29 and 49-53 is improper and unsustainable, and should be withdrawn. The Examiner has (i) failed to carry her burden of establishing a *prima facie* case based on supporting evidence and facts, (ii) improperly applied an *ipsis verbis* explicit claim term support requirement that does not exist under U.S. patent law and rules for assessing written description, and (iii) failed to view the specification and claims through the eyes of the skilled artisan versed in the mature and advanced art to which the invention relates. For any or all of these reasons, the written description rejection is improper and should be withdrawn.

The present claims are patentable and are in condition for immediate allowance. Withdrawal of the outstanding rejection is respectfully requested, and prompt allowance and issuance of the claims is earnestly solicited.

Similar issuance and allowance of the related parent case (USSN 10/175,486)(Atty. Docket No. CST-201) is also earnestly solicited, as the issues raised in the sole remaining written description rejection in that case are the same as those discussed in this paper.

If there are any questions regarding these amendments and remarks, the Examiner is requested to call the undersigned attorney at the telephone number provided.

Respectfully submitted,

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